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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,561	LOEWY ET AL.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-152* is/are pending in the application.

4a) Of the above claim(s) *86-124,127 and 148-152* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-85,125,126 and 128-147* is/are rejected.

7)☒ Claim(s) *81,125,126,132,133 and 138* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/22/04; 11/17/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-85, 125-126, 128-147 in the reply filed on April 5, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 86-124, 127, and 148-152 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 5, 2006.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Specifically, paragraph 93 contains the hyperlink http://www.idtdna.com.

Claim Objections

Claims 81, 132, 133, and 138 are objected to because of the following informalities: Claim 81 recites "the method according to claim 161". This claim appears to depend from claim 76. Claims 132 and 133 as recited depend from claim 127, but they appear be intended to depend from claim 128. Claim 138 recites "the method according to claim 138". This claim appears to depend from claim 137. Appropriate correction is required.

Claims 125 and 126 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16 and 22 recite the limitation "detecting the label" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 17-19 recite the limitation "the label" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 20 recites the limitation "the radioisotope" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 21 and 25 recite the limitation "the fluorophore" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 23-24 recites the limitation "the binding partner" in line 1. There is insufficient antecedent basis for this limitation in the claim.

It appears that the antecedent basis problems above may be the result of typographical errors, because: claim 16 seems to depend from claim 15, claims 17-20 appear to depend from claim 14, claim 21 appears to depend from claim 19, claim 22 appears to depend from claim 18, claims 23-24 appear to depend from claim 22, and claim 25 appears to depend from claim 24.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 6, 8-10, 12-28, 39, 41-43, 145, and 147 are rejected under 35 U.S.C. 102(b) as being anticipated by Giordano (US Patent No. 6,107,029).

Giordano teaches a method of detecting RNA-protein interactions (abstract).

Regarding claims 1 and 145, Giordano teaches a method for detecting a nucleic acid-binding protein comprising the steps of:

(a) contacting a nucleic acid molecule comprising a nucleic acid-binding sequence with a protein sample potentially containing an unknown nucleic acid-binding protein under conditions sufficient to form a binding complex, wherein the binding complex protects bound nucleic acid from degradation (column 7, lines 51-59; column 6, lines 1-10 teach unknown nucleic acid-binding proteins are present in the protein sample)

(b) subjecting the binding complex to nucleic acid degradation conditions which degrade any unbound nucleic acid molecules (column 9, lines 26-42)

(c) detecting any bound nucleic acid, wherein detecting said bound nucleic acid indicates a nucleic acid-binding protein (column 7, lines 12-14).

Further regarding claim 145 and also claims 2-3 and 147, Giordano teaches characterization of the nucleic acid binding protein using immunodetection (column 6, lines 44-50) or enzymatic digestion (column 11, lines 3-19), wherein the characterized nucleic acid binding protein constitutes the result of the assay.

Regarding claim 4, Giordano teaches that the immunodetection step comprises (see column 6, lines 44-50):

(a) contacting antibodies raised against known nucleic acid binding proteins with the nucleic acid binding proteins under conditions sufficient to form a protein-antibody complex

(b) detecting the protein-antibody complex

(c) characterizing the protein-antibody complex.

Regarding claims 6 and 8-10, Giordano teaches that the protein may be a purified protein, a partially purified protein, or a cell extract (column 6, lines 1-4). Giordano further teaches that the extracts may be prepared from human cell lines such as HeLa cells (column 12, lines 4-8).

Regarding claims 12-13, Giordano teaches that the nucleic acid is RNA, including synthetic RNAs (column 6, lines 51-55).

Regarding claims 14, 17-21, and 26-27, Giordano teaches that the nucleic acid molecule contains a label such as a radioisotope (such as 32P, 33P, 35S), biotin, a fluorophore (such as fluorescein, rhodamine, and Texas Red), or a dye (such as cyanine dyes or DAPI) (column 7, lines 12-22).

Regarding claims 15-16, Giordano teaches detection of the label using a fluorescence detection system, and enzyme detection system, a biotinylation detection system, or a radioactive detection system (column 7, lines 12-50 and column 8, line 45 – column 9, line 25).

Regarding claims 22-25, Giordano teaches that detecting the label further comprises contacting the biotin-labeled nucleic acid with a binding partner, specifically, streptavidin (column 7, lines 42-50). Giordano further teaches that the streptavidin may be labeled with a fluorophore such as Cy3.5 or Cy7 (column 7, lines 38-41).

Regarding claims 28, 39, and 41, Giordano teaches enzymatic degradation using RNase in an amount sufficient to degrade unbound nucleic acids (column 9, lines 26-42).

Regarding claims 42-43, Giordano teaches that the binding between the nucleic acid and protein may be specific or nonspecific (column 4, lines 24-44 teach detection of specific interactions; Figures 1-3 show detection of specific and non-specific interactions).

Claims 1-3, 6-19, 22-23, 26, 28-35, 37, 39-46, 50-62, 65-66, 69, 71-78, 80, 82-85, 128, 134-137, 139-140, 143, and 145-147 are rejected under 35 U.S.C. 102(e) as being anticipated by Heroux et al. (US Patent No. 6,312,896 B1).

Regarding claims 1, 44, and 139, Heroux teaches a method for detecting a nucleic acid-binding protein comprising the steps of:

(a) contacting a nucleic acid molecule comprising a nucleic acid-binding sequence with a protein sample potentially containing an unknown nucleic acid-binding protein under conditions sufficient to form a binding complex, wherein the binding complex protects bound nucleic acid from degradation (column 4, line 59 – column 5, line 4; column 16, lines 10-12 teach that the method may be used to identify DNA-binding proteins, and therefore, the sample may potentially contain an unknown nucleic acid-binding protein)

(b) subjecting the binding complex to nucleic acid degradation conditions which degrade any unbound nucleic acid molecules (column 5, lines 4-6)

(c) detecting any bound nucleic acid, wherein detecting said bound nucleic acid indicates a nucleic acid-binding protein (column 5, lines 6-8).

Figure 7 of Heroux also teaches the method of claim 1.

Further regarding claims 44, 139, and 143, Heroux teaches that steps corresponding to the instant claim 1 (discussed above) using a labeled nucleic acid substrate (column 17, lines 63-67) may be conducted in a reaction vessel comprising a plurality of wells (such as a microtiter plate, see column 7, lines 63-67), and further that the method is particularly suited to high-throughput applications (column 16, lines 14-15).

Regarding claims 2-3 and 45-46, Heroux teaches characterizing the nucleic acid-binding protein using mass spectroscopy (column 17, lines 17-31, in particular, line 22). Although Heroux teaches analysis of the nucleic acid substrates and/or products using mass spectroscopy, these measurements inherently provide a characterization (albeit an indirect one) of the nucleic acid-binding protein as well, specifically a suggestion of the nucleic acid sequence to which the protein binds.

Regarding claims 6 and 51, Heroux teaches that the protein may be a purified protein or a cell extract (column 24, lines 49-54).

Regarding claims 7-10 and 52-55, Heroux teaches the use of extracts prepared from prokaryotic cells, and HeLa cells, which are a human cell line (column 16, lines 21-29 teach that the proteins may be derived from bacteria; column 24, lines 49-54 teach the use of the HeLa cell extract).

Regarding claims 11-13 and 56, Heroux teaches that the nucleic acid may be RNA (see claim 11), or a synthetic DNA (column 23, lines 43-46).

Regarding claims 14, 17-19, 57, and 60-62, Heroux teach that the nucleic acid molecule contains a label such as a radioisotope, biotin, or a fluorophore (column 17, lines 63-67).

Regarding claims 15-16 and 58-59, Heroux teach detection of the label using a fluorescence detection system or an enzyme linked detection system (column 17, lines 63-67 teach the detectable labels; column 18, line 63 – column 19, line 32 teach fluorescence detection; column 18, lines 37-39 teach ECL detection).

Regarding claims 22-23 and 65-66, Heroux teaches that detecting the label further comprises contacting the biotin-labeled nucleic acid with a binding partner, specifically,

streptavidin (column 18, lines 37-40 teach an additional capture step; column 17, lines 35-39 teach a biotin-labeled nucleic acid substrate; column 12, lines 33-42 teach the use of streptavidin as a binding partner).

Regarding claims 26 and 69, Heroux teaches contacting the nucleic acid with a dye (column 10, lines 1-6, specifically the "organic laser dyes").

Regarding claims 28-30 and 71-73, Heroux teaches enzymatic degradation and physical degradation, separately and in combination. Heroux also teaches that the physical degradation conditions comprise heat and alkali in Maxim-Gilbert sequencing (column 16, lines 34-44).

Regarding claims 31-32 and 74-75, Heroux teaches that the nucleic acid comprising a chemical modification to one of the nucleotide bases (adenine, guanine, cytosine, thymine) that enables enzymatic degradation of the modified nucleic acid (column 16, lines 44-53).

Regarding claims 33-35 and 76-78, Heroux teaches the use of a DNA N-glycosylase, specifically, uracil DNA glycosylase, as the degradation enzyme (column 11, line 27).

Regarding claims 37 and 80, Heroux teaches that degradation of the nucleic acid molecule may consist of enzymatic and/or physical degradation steps (column 16, lines 32-44) and further teaches the use of the DNA N-glycosylase, uracil-DNA glycosylase (column 11, line 27). When uracil-DNA glycosylase is used as the cleavage agent, the base excision reaction inherently consists of the steps:

(a) contacting the nucleic acid molecule with the DNA N-glycosylase

(b) excising one or more nucleotide bases of the DNA molecule having the chemical modification;

(c) forming an AP site at each excised nucleotide base.

Then, regarding step (d), in order to effect degradation of the nucleic acid at the AP site introduced by uracil-DNA glycosylase, (the goal of the Heroux method), treatment with physical degradation reagents (heat and alkali) is inherently required.

Regarding claims 39-40 and 82-83, Heroux teaches contacting the binding complex with an enzyme (DNase) in an amount sufficient to degrade unbound nucleic acid molecules (see Table 1, column 24, lines 20-29, where DNase degrades nucleic acids unprotected by NFkB binding).

Regarding claim 41, Heroux also teaches the use of RNase (column 23, line 3).

Regarding claims 42-43 and 84-85, Heroux teaches that the binding between the nucleic acid and protein may be specific or nonspecific (column 16, lines 29-31).

Regarding claim 50, Heroux teaches the method of claim 44, further comprising binding the DNA molecule to a magnetic microparticle in the reaction vessel (column 23, lines 64-66).

Regarding claims 128, 134 and 135, the microtiter plate taught by Heroux (column 7, lines 63-67) is a strip well unit, because the microtiter plate comprises a linear arrangement of reaction wells and made from any known materials used in the art, such as, plastic (the specification's definition of the "strip well unit"). Also, the microtiter plate of Heroux is a planar well unit, because a microtiter plate comprises "a flat surface having an array of reaction wells and made from any known materials used in the art, such as, plastic" (the specification's definition of a "planar well unit".

Regarding claim 136, Heroux teaches using an array of immobilized nucleic acids to conduct the protein binding assay (column 9, lines 34-54). These arrays are chip well units.

Regarding claim 137, Heroux further teaches validating the detection of the nucleic acid-binding protein (Example 1, esp. column 24, lines 29-37, which teaches specificity controls).

Regarding claim 140, Heroux teaches hybridization of the nucleic acid to a generic capture reagent (column 18, lines 37-40 teach an additional capture step; column 17, lines 35-39 teach a biotin-labeled nucleic acid substrate; column 12, lines 33-42 teach the use of streptavidin as a binding partner; see also Figure 7).

Regarding claims 145 and 147, Heroux teaches a method of transmitting the result of an assay comprising:

(a) contacting a nucleic acid molecule comprising a nucleic acid-binding sequence with a protein sample potentially containing an unknown nucleic acid-binding protein under conditions sufficient to form a binding complex, wherein the binding complex protects bound nucleic acid from degradation (column 4, line 59 – column 5, line 4; column 16, lines 10-12 teach that the method may be used to identify DNA-binding proteins, and therefore, the sample may potentially contain an unknown nucleic acid-binding protein)

(b) subjecting the binding complex to nucleic acid degradation conditions which degrade any unbound nucleic acid molecules (column 5, lines 4-6)

(c) detecting any bound nucleic acid, wherein detecting said bound nucleic acid indicates a nucleic acid-binding protein (column 5, lines 6-8).

(d) characterizing the nucleic acid-binding protein using mass spectroscopy (column 17, lines 17-31, in particular, line 22), wherein the characterized nucleic acid binding protein constitutes the result of the assay.

Regarding step (d) above, although Heroux teaches analysis of the nucleic acid substrates and/or products using mass spectroscopy, these measurements inherently provide a characterization (albeit an indirect one) of the nucleic acid-binding protein as well, specifically a suggestion of the nucleic acid sequence to which the protein binds.

Regarding claim 146, Heroux teaches the use of a microtitier plate (column 7, lines 63-67).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4, 20-21, 24-25, 27, 47, 63-64, 67-68, and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heroux et al. (US Patent No. 6,312,896 B1) in view of Giordano (US Patent No. 6,107,029).

Heroux teaches the method of claims 1-3, 17, 19, 23, 26, 44-46, 60, 62, 65, and 69.

Heroux does not teach immunodetection using specific antibodies.

Although Heroux teaches the use of fluorescent, radioactive, and dye labels, specific examples of such labels are not taught.

Giordano teaches a method of detecting RNA-binding proteins. As discussed above, the method of Giordano anticipates the instant claims 1-4, 6, 8-10, 12-28, 39, 41-43, 145, and 147.

Regarding claims 4 and 47, Giordano teaches detection of DNA binding proteins using specific antibodies (column 6, lines 44-50).

Regarding claims 20 and 63, Giordano teaches labeling nucleic acids with the radioactive labels 33P, 32P, and 35S (column 7, lines 16-17).

Regarding claims 21, 24-25, 64, 67, and 68, Giordano teaches labeling of nucleic acids or a streptavidin capture reagent with fluorescent labels including fluorescein, Texas Red, fluorescein derivatives, and rhodamine (column 7, lines 17-20).

Regarding claims 27 and 70, Giordano teaches labeling nucleic acids with a dye such as a cyanine dye or DAPI (column 7, lines 21-21).

It would have been prima facie obvious for the person of ordinary skill in the art at the time of invention to apply the teachings of Giordano to the method of Heroux. Giordano taught that specific antibodies were useful for detection of nucleic acid binding proteins (column 6, lines 44-50). This would have provided motivation for the ordinary practitioner of the method of

Heroux to alternatively or additionally include antibody-based methods for the detection, and in particular, for the identification of nucleic acid binding proteins. The ordinary practitioner of the method of Heroux would also have been motivated to label the nucleic acids using any of the specific examples of radioactive, fluorescent, or dye labels taught by Giordano. Giordano taught that nucleic acid detection was facilitated by using well known labeling techniques and provided several examples of each type of label contemplated by Heroux (column 7, lines 12-41). The ordinary practitioner would have been motivated by the teachings of Giordano to utilize any of the exemplary radioactive, fluorescent, or dye labels in order to detect nucleic acids in the method of Heroux. Finally, the teaching by Giordano that the fluorescent dyes "Cy3.5 and Cy7 are available as avidin or anti-digoxygenin conjugates for secondary detection of biotin- or digoxygenin labeled probes", would have provided motivation for the ordinary artisan to include a fluorescent label on the streptavidin binding partner in the detection method of Heroux to provide a secondary means of nucleic acid detection.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Giordano (US Patent No. 6,107,029) in view of Buratowski et al. (Current Protocols in Molecular Biology, 1996).

Giordano teaches the method of claim 4, as discussed above.

Giordano teaches immunodetection with specific antibodies, but does not specifically teach that the protein-antibody complex further comprises the bound nucleic acid.

Buratowski teaches an "antibody supershift assay" method to identify a nucleic acid binding protein (pages 12.2.5-12.2.6). Briefly, the method comprises reacting a nucleic acid sample, a sample containing the nucleic acid-binding protein, and an antibody specific for the

nucleic acid binding protein followed by non-denaturing gel electrophoresis. The nucleic acid binding-protein is identified based on its ability to shift the radiolabeled nucleic acids to a higher molecular weight species by formation of a specific nucleic acid-protein complex. The inclusion of an antibody specific to the protein produces a further upward shift in the molecular weight – a "supershift" – due to the formation of a nucleic acid-protein-antibody ternary complex.

Regarding claim 5, the protein-antibody complex taught by Buratowski further comprises the bound nucleic acid molecule (page 12.2.5).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to incorporate the antibody supershift assay taught by Buratowski into the method of Giordano. The method of Giordano utilized electrophoretic mobility shift assays to identify RNA-protein interactions (see for example, column 8, line 63 – column 9, 25). These assays of Giordano are essentially equivalent to the Basic Protocol taught by Buratowski (pages 12.2.2 – 12.2.5). Buratowski also taught that including an antibody specific for a nucleic acid-binding protein allowed identification of the protein in the nucleic acid-protein complex based on the observation of an additional molecular weight shift (see Alt. Protocol 2, pages 12.2.5 – 12.2.6). This would have strongly motivated the ordinary practitioner of the method of Giordano to adapt the basic mobility shift assay protocol as suggested by Buratowski, in order to identify the nucleic acid binding protein in a single reaction, rather than via the subsequent immunodetection step proposed by Giordano (column 6, lines 44-50).

Claims 5 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heroux et al. (US Patent No. 6,312,896 B1) in view of Giordano (US Patent No. 6,107,029) and further in view of Buratowski et al. (Current Protocols in Molecular Biology, 1996).

The combined teachings of Heroux and Giordano result in claims 4 and 47, as discussed above.

Neither Heroux nor Giordano teaches that the protein-antibody complex also includes the bound nucleic acid.

Buratowski teaches an "antibody supershift assay" method to identify a nucleic acid binding protein (pages 12.2.5-12.2.6). Briefly, the method comprises incubating a nucleic acid sample, a sample containing the nucleic acid-binding protein, and an antibody specific for the nucleic acid binding protein followed by non-denaturing gel electrophoresis. The nucleic acid binding-protein is identified based on its ability to shift the radiolabeled nucleic acids to a higher molecular weight species by formation of a specific nucleic acid-protein complex. The inclusion of an antibody specific to the protein produces a further upward shift in the molecular weight – a "supershift" – due to the formation of a nucleic acid-protein-antibody ternary complex.

Regarding claims 5 and 48, the protein-antibody complex taught by Buratowski further comprises the bound nucleic acid molecule (page 12.2.5).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to incorporate the teachings of Buratowski into the combined method of Heroux and Giordano. Buratowski taught that including an antibody specific for a nucleic acid-binding protein in a reaction mixture comprising the nucleic acid and nucleic acid-binding protein allowed rapid, single-step identification of the nucleic acid-binding protein based on detection of

the resulting nucleic acid-protein-antibody ternary complex (page 12.2.5). This would have strongly motivated the ordinary practitioner of the combined method of Giordano and Heroux to incorporate antibody-based detection of the protein-nucleic acid complexes in order to rapidly identify the protein component of the complex in a single reaction step, rather than the additional antibody detected step suggested by Giordano (column 6, lines 44-50). Finally, although the teachings of Buratowski were presented in the context of electrophoresis-based assays, the ordinary practitioner would nevertheless have been motivated to utilize specific antibodies to identify the protein component of the protein-nucleic acid complexes formed in the microplate-based method of Heroux.

Claims 36, 38, 79, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heroux et al. (US Patent No. 6,312,896 B1) in view of Hoffman et al. (US Patent No. 6,048,696).

Heroux teaches the method of claims 33-35, 37, 76-78, and 80, as discussed above.

Heroux teaches the use of uracil DNA glycosylase. This enzyme does not possess AP lyase activity, nor does Heroux teach use of another enzyme with AP lyase activity.

Regarding claims 38 and 81, Heroux teaches that degradation of the nucleic acid molecule may consist of enzymatic and/or physical degradation steps (column 16, lines 32-44) and further teaches the use of the DNA N-glycosylase, uracil-DNA glycosylase (column 11, line 27). When uracil-DNA glycosylase is used as the cleavage agent, the base excision reaction inherently consists of the steps:

(a) contacting the nucleic acid molecule with the DNA N-glycosylase

(b) excising one or more nucleotide bases of the DNA molecule having the chemical modification;

(c) forming an AP site at each excised nucleotide base.

Then, regarding step (d), in order to effect degradation of the nucleic acid at the AP site introduced by uracil-DNA glycosylase, (the goal of the Heroux method), treatment with physical degradation reagents (heat and alkali) is inherently required.

Hoffman teaches a method of analyzing a DNA molecule using the enzyme formamidopyrimidine DNA N-glycosylase (Fapy or Fpg) (see abstract).

Regarding claims 36 and 79, Fapy possesses DNA N-glycosylase activity and AP lyase activity (column 4, lines 22-28).

Regarding claims 38 and 81, Hoffman teaches that the Fapy enzyme possesses DNA N-glycosylase activity and AP lyase activity, thereby enabling the base excision and strand cleavage activity to occur using a single enzyme (column 9, lines 1-6). Hoffman explicitly states, "Preferably the enzyme is foramidopyrimidine DNA N-glycosylase (FPG protein), since both N-glycosylase and AP lyase activities reside in the same molecule, that it, only a single enzyme is required" (column 9, lines 12-16). In addition, Hoffman teaches that unlike uracil DNA-glycosylase, which only recognizes misincorporated uracil, the FPG protein recognizes a diverse group of modifications to nucleic acids (see column 4, lines 19-21 and lines 38-48).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to substitute the uracil DNA-glycosylase taught by Heroux with the FPG protein taught by Hoffman. Hoffman expressly taught the advantages of using the FPG protein to catalyze

enzymatic degradation and repair of modified DNA, namely: (1) the ability to use a single enzyme to catalyze base excision and strand cleavage (column 9, lines 12-16), and (2) the ability to effect cleavage at a diverse group of modified nucleic acid bases (column 4, lines 19-21 and 38-48). These teachings of Hoffman would have strongly motivated the ordinary practitioner of the method of Heroux to substitute the FPG protein for uracil DNA glycosylase in order to achieve the following advantages: (1) a simplified assay where only one enzyme is required for base excision and strand cleavage, (2) elimination of the need to optimize reaction conditions for multiple enzymes with DNA N-glycosylase and AP lyase activity, (3) ability to effect degradation of a wider variety of unprotected (unbound) modified nucleic acids due to the wider substrate recognition properties of FPG.

Claims 49, 129-133, and 144 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heroux et al. (US Patent No. 6,312,896 B1) in view of Shao et al. (US Patent No. 6,703,203 B2).

Heroux teaches the method of claims 44, 128, and 139, as discussed above.

Heroux teaches high throughput screening, but does not explicitly teach automation.

Heroux teaches detection using microplates, but specific numbers of wells are not taught.

Shao teaches an automated high-throughput screening method for detection of specific binding interactions, including protein-DNA interactions (abstract and column 11, lines 39-54).

Regarding claims 49 and 144, the method of Shao is automated (column 2, lines 44-46).

Regarding claims 129-133, Shao teaches conducting the high throughput screening assay in microplates having 96 wells, 384, wells, or 1536 wells (column 2, lines 40-42).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to automate the method of Heroux and utilize microplates having for example, 96 or 384 wells in view of the teachings of Shao. Shao stated the use of 96-well, 384-well, and 1536-well plates in the high throughput interaction screening assay "facilitates simple, highly efficient, and automatic maniupulation such as sample handling and washing by robotics" (column 2, lines 44-46). Shao further taught that the method was useful in detection of protein-DNA interactions (column 11, lines 39-54). These teachings of Shao would have motivated the ordinary practitioner of the DNA-binding protein identification method of Heroux to utilize the microtiter plate configurations taught by Shao in order to facilitate automation of the method, thereby increasing the reproducibility between assays, minimizing the required "hands on" time, and simplifying the method.

Claim 138 is rejected under 35 U.S.C. 103(a) as being unpatentable over Heroux et al. (US Patent No. 6,312,896 B1) in view of Wang et al. (US Patent No. 5,922,617).

Heroux teaches the method of claim 137, as discussed above.

Regarding claim 138, Heroux teaches a method comprising:

(a) contacting a nucleic acid molecule comprising a nucleic acid-binding sequence with a protein sample potentially containing an unknown nucleic acid-binding protein in a reaction vessel comprising a plurality of wells (column 4, line 59 – column 5, line 4; column 16, lines 10-12 teach that the method may be used to identify DNA-binding proteins, and therefore, the sample may potentially contain an unknown nucleic acid-binding protein; column 7, lines 63-67 teach use of a microplate in the assay)

(b) exposing the DNA molecule and the protein sample in the reaction vessel to conditions sufficient to form a binding complex, wherein the binding complex protects the nucleic acid from degradation (column 4, line 59 – column 5, line 4)

(c) subjecting the binding complex to nucleic acid degradation conditions which degrade any unbound nucleic acid molecules (column 5, lines 4-6)

(d) detecting any bound nucleic acid, wherein detecting said bound nucleic acid indicates a nucleic acid-binding protein (column 5, lines 6-8), wherein the method is high throughput (column 16, lines 14-15).

Heroux does not teach performing a series of washes of increasing stringency to eliminate non-specific binding interactions.

Wang teaches a solid-phase method for detecting interactions between compounds including DNA-protein interactions (see column 1, line 65 – column 2, line 15 and column 7, lines 52-56). Wang also teaches performing washes of increasing stringency to reduce non-specific interactions, between complexes that include DNA-binding protein-DNA complexes (column 9, line 56 – column 10, line 19). In particular, Wang states, "After the incubation period, the solid substrate surface may be washed to remove non-specifically bound entities, to enhance the stringency of hybridization, to wash away interfering materials, and the like. One or more washings may be employed with varying degrees of vigor, depending on the nature of the components, the degree of affinity between the bound and mobile component and the manner in which the bound component is bound to the solid substrate surface" (column 9, line 61 – column 10, line 2).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to incorporate a series of washes at increasing levels of stringency in the method of Heroux to eliminate non-specific binding interactions, and thereby, improve the results obtained. As discussed above, Wang particularly pointed out that a series of washes of increasing stringency were useful in eliminating non-specific interactions that may occur between a DNA-binding protein and a nucleic acid (column 9, line 56 – column 10, line 19). The ordinary practitioner of the method of Heroux would have been motivated by these teachings of Wang to incorporate multiple rounds of increased stringency binding in order to eliminate non-specific interactions that may occur between a potential DNA-binding protein and its nucleic acid binding partner, and thereby, improve the accuracy of the results obtained.

Allowable Subject Matter

The following is a statement of reasons for the indication of allowable subject matter: Claims 141 and 142 contain allowable subject matter. Regarding claim 141, the prior art neither teaches nor suggests the use of a generic capture reagent comprising a poly(A) sequence conjugated to immobilized IgG. Regarding claim 142, the prior art of VanderBorght et al. (Journal of Immunological Methods, 1999) teaches an ELISA method utilizing microplates coated with anti-FITC to detect FITC-labeled oligonucleotides (see Figure 1). However, claim 142 depends from claim 141, which contains allowable subject matter, as noted above.

Conclusion

No claims are currently allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Numerous references teach identification of nucleic-acid binding proteins based on detection of a protected nucleic acid including: Edwards et al. (US Patent No. 5,306,619), Church et al. (US Patent No. 6,548,021 B1), Leblanc et al. (2000; cited in IDS), Taylor et al. (2000; cited in IDS), Phillipe et al. (2000; cited in IDS), Zhou et al. (US 2003/0104368 A1), and Clausen et al. (US 2003/0215854 A1). As noted above, the prior art of VanderBorght et al. teaches the use of anti-FITC coated microplates in an ELISA method to detect FITC-labeled oligonucleotides.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is (571) 272-8291. The examiner can normally be reached on M-F 7:30-5 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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